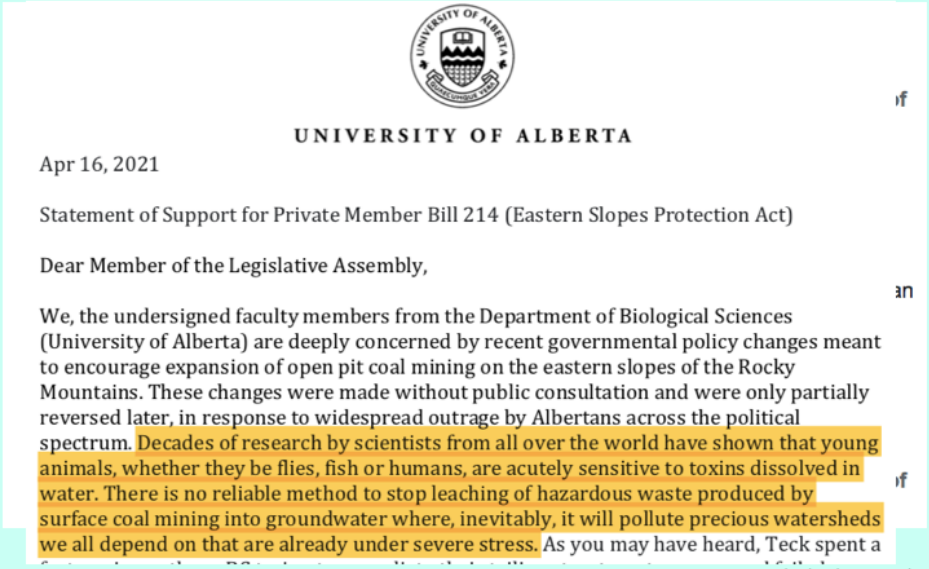
# Biological Checkpoints and Coal Mines

CPC presentation: Shelagh Campbell_July6,2021

While the title of my talk is “Biological Checkpoints and Coal Mines” this image I’ve chosen to start with represents my personal connection to the eastern slopes. Its one of my favorite pictures of a glorious day spent whitewater kayaking with friends on the Whirlpool River in Jasper, a river that is protected by its location in a National park. Like all of you here, people living in Alberta are very proud of our beautiful mountain landscapes and the clean fresh water they provide that we all depend on.

# Why am I consulting with you?



UNIVERSITY OF ALBERTA

Apr 16, 2021

Statement of Support for Private Member Bill 214 (Eastern Slopes Protection Act)

Dear Member of the Legislative Assembly,

We, the undersigned faculty members from the Department of Biological Sciences (University of Alberta) are deeply concerned by recent governmental policy changes meant to encourage expansion of open pit coal mining on the eastern slopes of the Rocky Mountains. These changes were made without public consultation and were only partially reversed later, in response to widespread outrage by Albertans across the political spectrum. Decades of research by scientists from all over the world have shown that young animals, whether they be flies, fish or humans, are acutely sensitive to toxins dissolved in water. There is no reliable method to stop leaching of hazardous waste produced by surface coal mining into groundwater where, inevitably, it will pollute precious watersheds we all depend on that are already under severe stress. As you may have heard, Teck spent a

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Last April I asked members of my department at Uof A to consider signing a letter I had written on behalf of private members bill to protect the Eastern slopes from coal mining. This letter, which will be included in my written submission, got some attention in the Canadian press. This, I imagine, is where my invitation to speak to you today came from.

I don't know if you have read it, but our letter was meant to draw attention to the known harmful effects of surface coal mining. In particular, it drew attention to the well known sensitivity of early animal development to environmental toxins, with selenium being of particular concern.


Each of the 35 biologists who signed this letter have PhD degrees with many years of research experience and many are very prominent Canadian scientists whose work is internationally recognized. We work in many different areas of the Biological Sciences, some which are <u>obviously</u> relevant to coal policy such as Environmental toxicology, Aquatic ecosystems and Wildlife Conservation. Although this group of highly trained scientists have many different perspectives on issues relating to coal mining, we all all know that: Water is Life.

## What **IS** a checkpoint?


https://www.chicagotribune.com/investigations/ct-dui-checkpoints-suburbs-met-20150507-story.html

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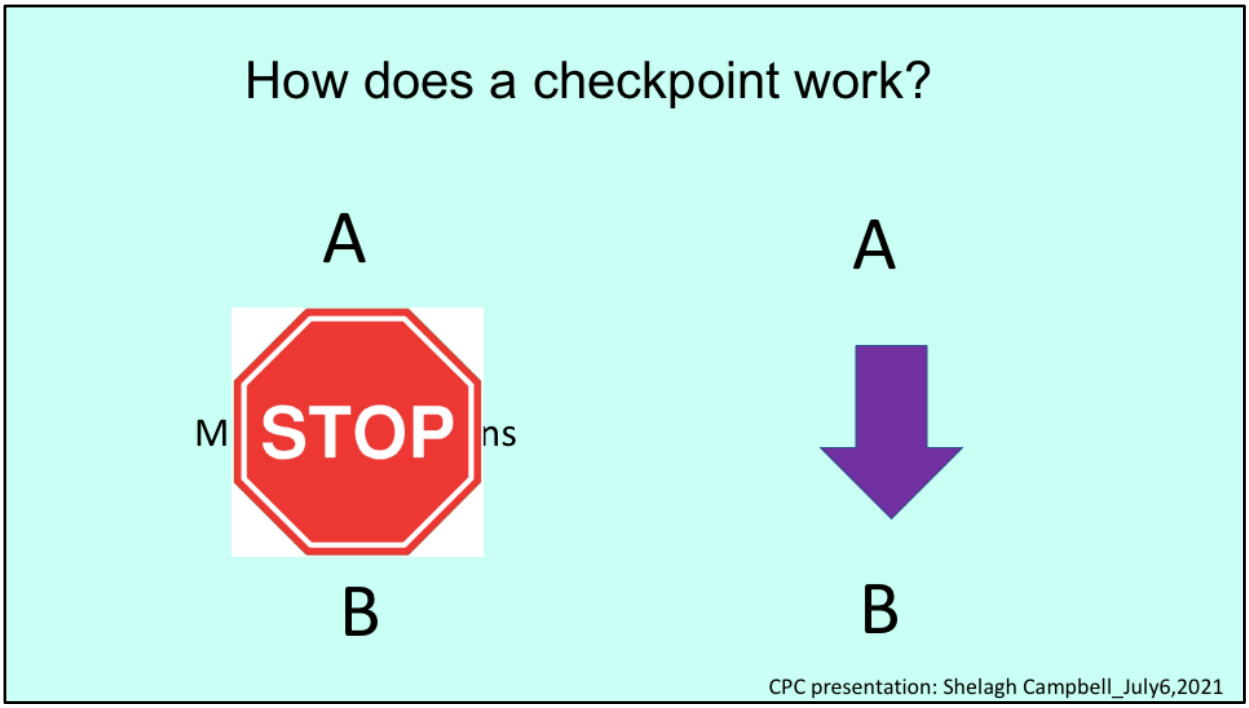
Why is the title of my presentation about biological checkpoints and how are they relevant to Coal Policy? We are all familiar with the concept of traffic checkpoints, for example police checking for drivers for impairment or signs that prevent people from driving the wrong way on logging roads. These are mechanisms used for preventing predictable events with catastrophic consequences from happening.




The basic idea of a checkpoint mechanism is very simple. By monitoring data which is relevant to a given situation, well informed decisions can be made about whether it is safe to progress from one point to the next. We do this all the time, often subconsciously. For example, is it safe to cross the street?
Under unsafe conditions, for example if a driver is found to be drunk, a functional checkpoint can prevent that person from harming themselves or others.

## Why does checkpoint failure matter?

https://edmontonjournal.com/news/local-news/34-avenue-closed-as-edmonton-police-investigate-collision-that-left-man-critically-injured

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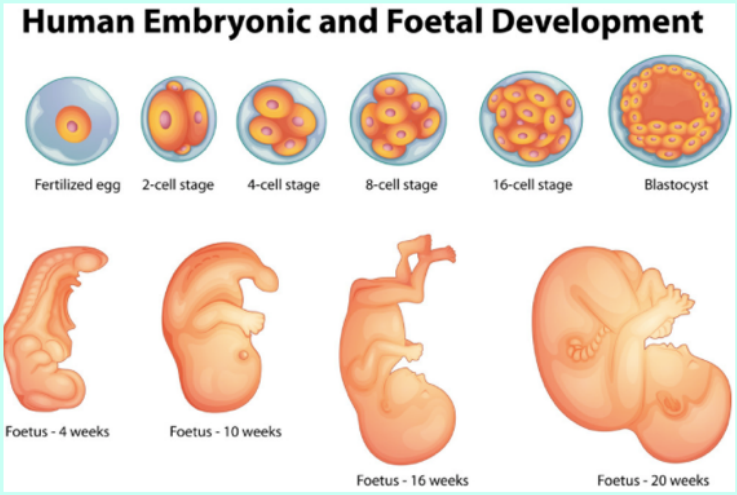
It is important to note that the predictable events which checkpoints are meant to prevent aren't necessarily inevitable – not every drunk driver will causes an accident, for example. So, you might argue that it is not really worth the effort and cost of setting up a checkpoint. We all know what can happen when an impaired driver gets behind the wheel, however. So to reiterate, the point of a checkpoint is to use verifiable evidence ahead of time to prevent catastrophic events from happening, later.

## Biological Checkpoint Mechanisms




https://www.vectorstock.com/royalty-free-vector/stages-in-human-embryonic-development-vector-1855660

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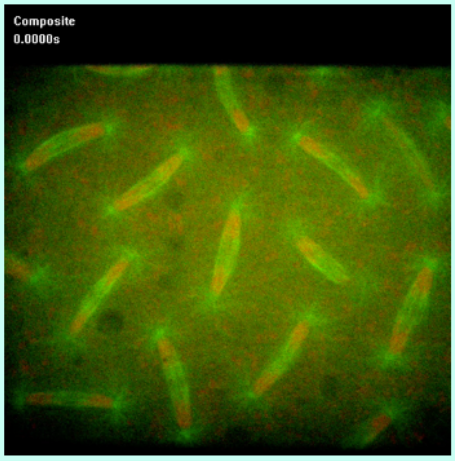
From the examples I've presented so far, you might think that 'humans' invented checkpoints. In fact, biological checkpoint mechanisms probably emerged very early in the evolution of multicellular organisms, hundreds of millions of years ago. For example, conserved cell cycle checkpoint mechanisms are used for coordinating the development of all animals, including humans, as shown here. Without going into too much detail, these cell cycle checkpoint mechanisms ensure that we develop limbs and organs of appropriate size, in correct locations. Life as we know it would be impossible without these biological checkpoint mechanisms for coordinating all of the incredible complexity of animal development.

# Cell Cycle Checkpoint Mechanisms

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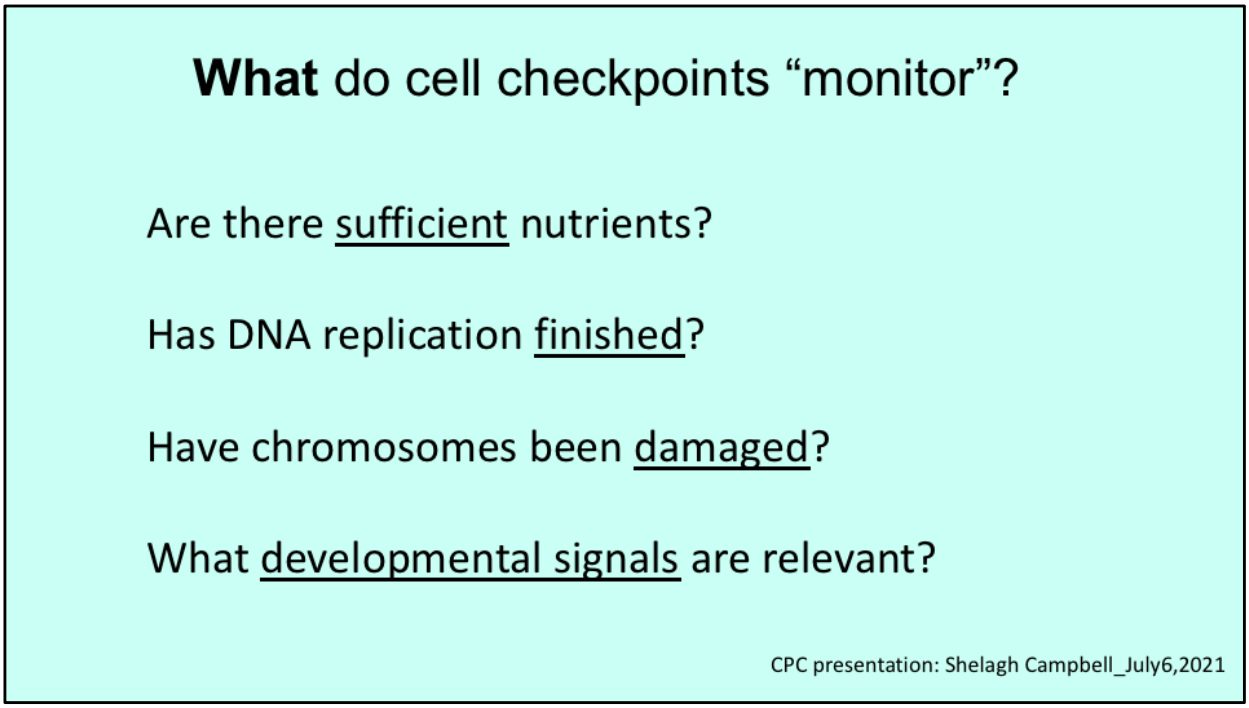
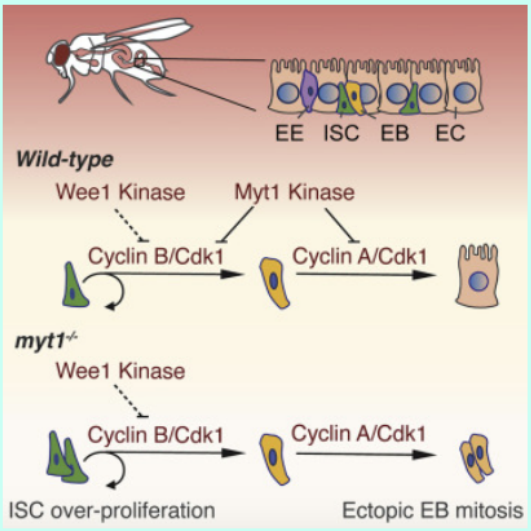
My particular area of research expertise is the cell cycle checkpoint mechanisms that monitor whether cells are 'ready' for mitosis, the process where duplicated chromosomes and organelles are partitioned into daughter cells by cell division as you may recall learning in high school biology courses.
To illustrate how this works I'm showing you a time-lapse movie made in our lab showing part of a fly embryo with fluorescently labeled microtubules and chromosomes as it progresses through embryonic cycles 10-13. At this early stage of embryonic development, these cell cycles are rapid and synchronous but slow down as they proceed, as if a brake is being gingerly applied. All animals undergo rapid cell cycles during early development with similarly precise temporal and spatial control of complex, inter-connected events and so it is not surprising that embryos of all animal species are extremely sensitive to toxins, such as selenium, in their environment.




You might be wondering 'What' types of information are monitored by cell cycle checkpoints to coordinate the process of development? There is no simple answer to this question, but here is a partial list. Basically, cells need to decide whether conditions are suitable for progressing through the cell cycle – or not. My research at the UofA has focused on enzymes that act like 'brakes' to the cell cycle, preventing entry into mitosis when cells are unprepared or damaged in some way that needs to be repaired. This last point on the list is important for it covers a complex topic of cell signaling that is used to balance cell numbers and control cell differentiation, so that our bodies maintain function throughout our lifetimes.

## Checkpoint regulation by Wee1 and Myt1 kinases




Willms, Zhou and Campbell., *Cell Reports*, 2020

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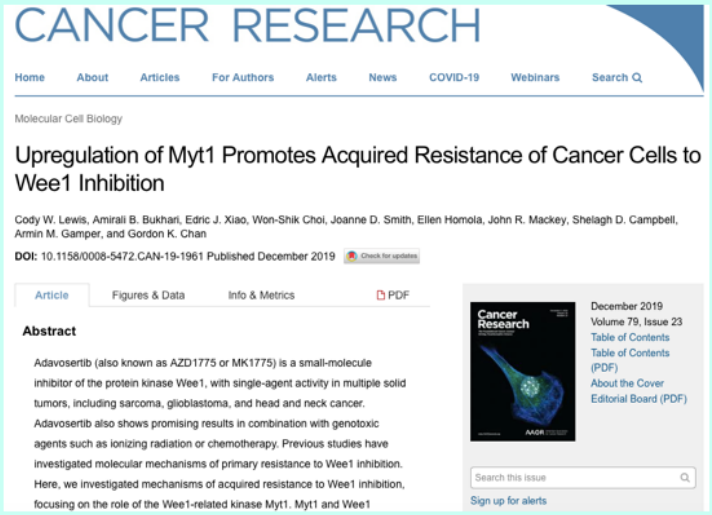
The epithelia in our guts, for example, is constantly being damaged and must be regenerated so as to fulfill its function of absorbing food while maintaining a barrier to infection. Using genetically engineered fruit flies we studied how checkpoint enzymes that function like cell cycle 'brakes' affect this process of gut regeneration and we published my graduate student's discoveries about this process, last fall. I'll include this document in my written submission.

## What **happens** when cell cycle checkpoints fail?



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Molecular Cell Biology

Upregulation of Myt1 Promotes Acquired Resistance of Cancer Cells to Wee1 Inhibition

Cody W. Lewis, Amirali B. Bukhari, Edric J. Xiao, Won-Shik Choi, Joanne D. Smith, Ellen Homola, John R. Mackey, Shelagh D. Campbell, Armin M. Gamper, and Gordon K. Chan

DOI: 10.1158/0008-5472.CAN-19-1961 Published December 2019

Article Figures & Data Info & Metrics PDF

Abstract

Adavosertib (also known as AZD1775 or MK1775) is a small-molecule inhibitor of the protein kinase Wee1, with single-agent activity in multiple solid tumors, including sarcoma, glioblastoma, and head and neck cancer. Adavosertib also shows promising results in combination with genotoxic agents such as ionizing radiation or chemotherapy. Previous studies have investigated molecular mechanisms of primary resistance to Wee1 inhibition. Here, we investigated mechanisms of acquired resistance to Wee1 inhibition, focusing on the role of the Wee1-related kinase Myt1. Myt1 and Wee1

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Lewis, et al., 2019

https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancers-grow

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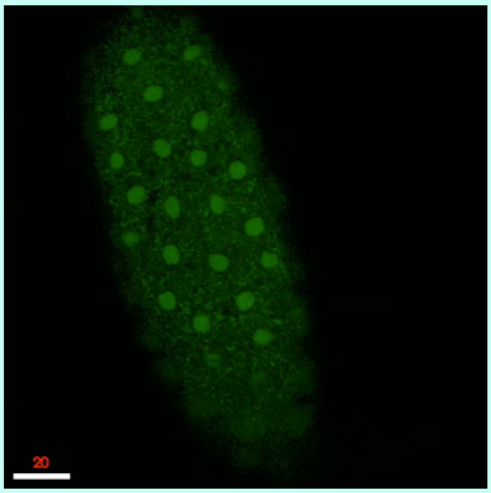
We also know that checkpoints are essential for maintaining the size and function of organs and tissues throughout our lifetimes. Indeed, one of the earliest signs of cells becoming cancerous is a loss of checkpoint control, no longer recognizing or responding to signals that would normally tell them to stop proliferating.

While this has not been the central focus of the research in my lab, I recently co-authored a manuscript with colleagues here at the Cross Cancer Institute about exploiting this defect to treat cancer by inhibiting a checkpoint enzyme we have worked on for many years called Wee1. I will also attach this manuscript to my written submission.

## Early embryo pre-mitotic checkpoints




Time lapse of cycles 10-13 in WT embryo labeled with fluorescent chromosomes.

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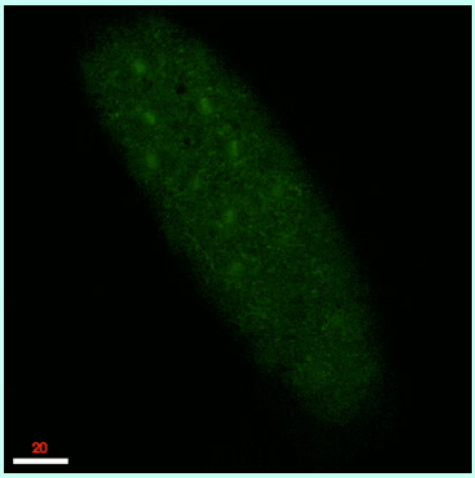
A more fundamental function of this enzyme Wee1 has fascinated me for many years and been a major focus of my research here at the UofA.

To illustrate this I will tell you more about how a normal fly embryo goes through cycles 10-13, which is a critical stage of development for the Wee1 checkpoint to function. In this movie I made over 20 years ago, the green fluorescence marks chromosomes as they replicate and then condense before dividing into two daughter nuclei. In a stunning feat of exponential growth, a fertilized fly embryo normally goes from one nucleus to roughly 6000 in two hours! The gradual lengthening of cycles 10-13 that you can observe here is the consequence of Wee1 'tapping on the brakes' to prevent mitosis from occurring before DNA replication is completed.

## What happens when embryo checkpoints fail?




Time lapse of cycles 10-13 in *wee1* mutant embryo.

*Price et al., 2000*

**Mitotic Catastrophe**

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We used genetic mutants that lack a functional Wee1 enzyme made by my first graduate student to study its role in this process when I first came to UofA.
Up until cycle 11, the mutant embryos look perfectly normal, cycling synchronously just like normal embryos. When these mutant embryos enter mitosis 11, however something goes drastically wrong. Because they lack a functional checkpoint 'brake" mechanism, they reach a critical timing threshold where DNA replication cannot be completed before the embryo begins mitosis. You don't need to be a developmental geneticist to see that when they reach that point the consequences are catastrophic. This absolute dependence on Wee1 during the rapid cleavage cycles is one reason why embryos of all species are so acutely sensitive to toxins like selenium, in their

environment.

## How do Checkpoints relate to Coal Policy?

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The eastern slopes of the Rockies contain large deposits of coal that have been mined since Europeans first settled in Alberta. The beauty and integrity of these mountains is central to the identity of First Nations and all Canadians, with people coming from all over the world to see these natural wonders. These landscapes contain the headwaters of rivers we all depend on to live that are also home to iconic and endangered wildlife. It took a leader of the stature of Peter Lougheed to develop the Coal Policy of 1976, which was a landmark example for its time in basing decisions about where coal mining would be allowed because of effects on the environment. The result of this policy was to restrict development of surface coal mining to certain areas of the eastern slopes that were deemed less 'sensitive' to this activity was it was noted was 'in conflict with virtually every other use to which the slopes might be put". The 1976 policy was, in effect, a checkpoint to coal development.

## 40+ years later…

https://www.scientificamerican.com/article/the-other-reason-to-shift-away-from-coal-air-pollution-that-kills-thousands-every-year/

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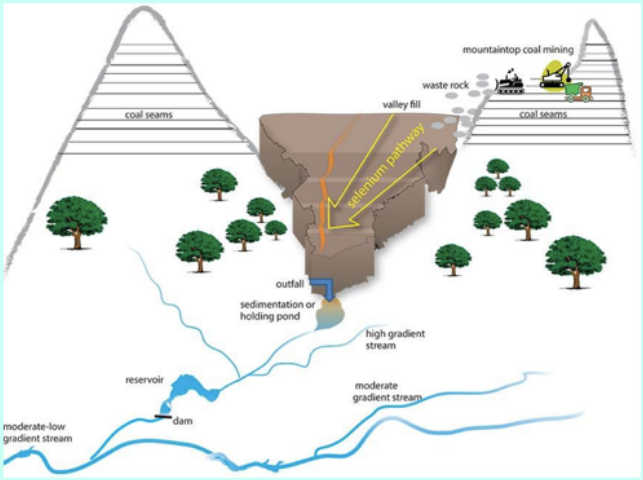
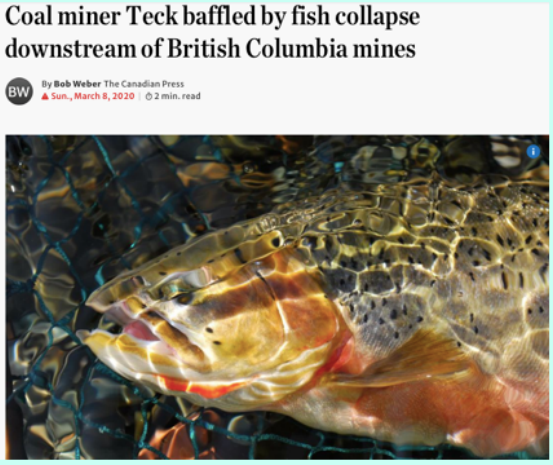
We have learned a lot in the 40 years since the original Coal Policy was adopted. We now know that **Coal consumption** is the single biggest contributor to anthropogenic **climate change**, responsible for almost half of total carbon dioxide emissions worldwide. As Canadians we should to be helping to solve this existential threat, instead of actively making it worse. While our local air quality here in Alberta improves as we shift away from coal burning towards other forms of electricity generation, our outsized carbon footprint from mining and shipping coal to other countries to manufacture goods that we then transport back here, is nothing to be proud of. Moreover, it reeks of hypocrisy for us to then complain about other countries burning coal at a time when we desparately need a global response to the crisis we are so clearly in, right now.

## Water is Life



Coal miner Teck baffled by fish collapse downstream of British Columbia mines

By Bob Weber The Canadian Press
Sun., March 8, 2020 | 2 min. read

https://www.usgs.gov/mission-areas/water-resources/science/linking-selenium-sources-ecosystems-mining?qt-science_center_objects=0#qt-science_center_objects

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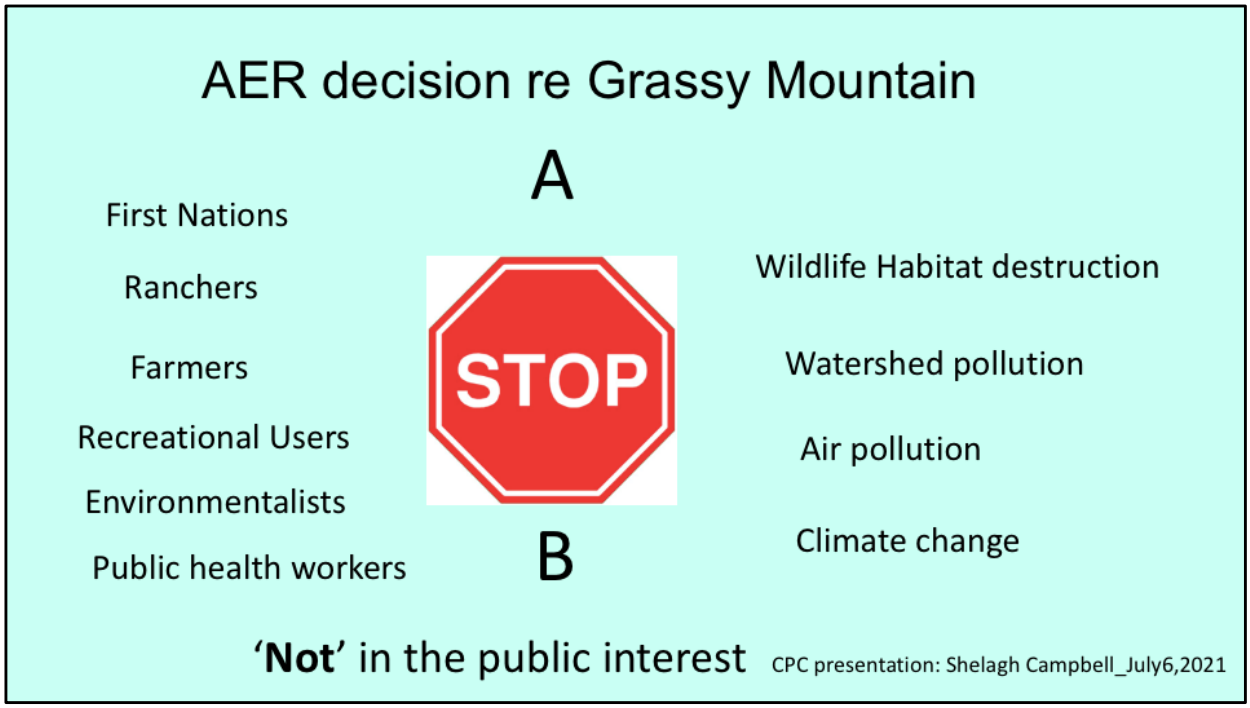
The indirect effects of coal mining on the environment and watersheds due to road building, clearcutting and erosion were also not as well understood 40 years ago as they are now. And, although the 1976 policy was developed by extensive, public consultation with a wide range of experts it did not address the concerns of First Nations peoples, which were not recognized at the time. Nor were the effects of selenium bioaccumulation in living organisms understood, then. We don't have those excuses any longer. Winds blow coal dust, tailings ponds leak and remediation costs money, lots of it. Despite the cheery claims made by coal mining companies and their lobbyists, no reliable technology exists for prevent such toxins from leaching into the water, and then inevitably, downstream. Is such a destructive industry really worth poisoning our precious Alberta aquifers

and watersheds?




We were pleasantly surprised recently that the AER fulfilled its stated mandate of "conserving water resources, managing public lands, and protecting the environment" by taking into account these issues I just mentioned in its decision to deny approval for the Grassy Mountain project. While this site was not itself protected by the original coal policy because of its long history of coal mining, we all knew the decision could have a huge impact on the surge of new projects that were already lined up and ready to go, just as the Alberta provincial government summarily rescinded the 1976 Coal policy without any public consultation, last spring.

As you know there has been widespread outrage as people from many walks of life across the province realized the implications of this act, prompting the government to

temporarily halt further progression and promise to conduct some form of public consultation. The same arguments presented to the joint provincial-federal review panel to deny the Grassy Mountain project approval of course also apply to all of these other projects. Coal mines are not in the public interest, being in the words of the original 1976 policy: “in conflict with with virtually every other use to which the slopes might be put”.

## What we Need is a Coal **Restriction** Policy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In view of these facts I argue that you should recommend the enactment of a Coal policy 'checkpoint' that completely bans coal mining on the eastern slopes. I support the High River mayor's proposed Alberta Coal Restriction Policy that many municipalities have already signed on to , stating these three key principles:

1) no further coal exploration or development should be permitted on the eastern slopes,

2) existing coal mining operations should be wound down as soon as possible

3) there should be immediate reclamation and remediation of lands recently disturbed by coal exploration activities

These principles recognize the inherent value of the eastern slopes and the headwaters they nourish. These landscapes are

critical to Alberta's identity and its future. The well documented negative effects of coal mines on the environment, human health and animal health all have to be taken into consideration for a truly modern Alberta coal policy for the 21st century. Water is Life.